Novel approach to control false positive rate in fuzzy cluster analysis of fMRI

Hesamoddin Jahanian[a,b], Hamid Soltanian Zadeh[¤a,b,c], Gholam A. Hossein-Zadeh[a]

[a]Control and Intelligent Processing Center of Excellence, Elec. and Comp. Eng. Dept., Faculty of Engineering, University of Tehran, Tehran 14399, Iran

[b]School of Cognitive Science, Institute for Studies in Theoretical Physics and Mathematics, Tehran, Iran

[c]Image Analysis Lab., Radiology Department, Henry Ford Health System, Detroit, MI 48202, USA

ABSTRACT

Fuzzy c-means (FCM) suffers from some limitations such as the need for *a priori* knowledge of the number of clusters, and unknown statistical significance and instability of the results, when it is applied to the raw fMRI time series. Based on randomization, we developed a method to control the false positive detection rate in FCM and estimate the statistical significance of the results. Using this novel approach, we proposed an fMRI activation detection method which uses FCM with controlled false positive rate. The ability of the method in controlling the false positive rate is shown by an analysis of false positives in activation maps of resting-state fMRI data. Controlling the false positive rate allows comparison of different feature spaces and fuzzy clustering methods. A new feature space, in multi and scalar wavelet domain, is proposed for activation detection in fMRI to address the stability problem. Finally, using the proposed method for controlling the false positive rate, the proposed feature space is compared to the cross-correlation feature space.

Keywords: fMRI, fuzzy clustering, statistical test, randomization, wavelets.

1. INTRODUCTION

Functional magnetic resonance imaging (fMRI) is a non-invasive technique for investigating the functional anatomy of the human brain using fast MRI data acquisition methods. A variety of analysis methods have been developed for detecting brain activations in fMRI. Principal component analysis (PCA),[1] independent component analysis (ICA),[2] and fuzzy C-Means clustering[3] are examples of model-free and nonparametric data driven methods for analyzing the fMRI data. They do not need any prior knowledge about the experiment or the hemodynamic response. Based on these methods, the data are classified into different groups. Usually, the contents of one class are interpreted as activation.

In neuro-imaging, model-free analysis has been mostly carried out using clustering methods. The aim of clustering techniques is identifying regions with similar patterns of activation. The most popular clustering method is the fuzzy C-means (FCM) algorithm.[4] An important limitation of FCM and other clustering techniques is their inability to assign statistical significance to the results. The FCM generates the membership maps of the brain voxels to different clusters. After the FCM convergence, the cluster with the most similar centroid to the stimulation pattern is selected as the active cluster and the membership degree of each voxels to this cluster (u) is compared with a threshold u_a in order to detect activated voxels. By comparing u at each voxel with threshold u_a, one tests the null hypothesis H_0: "no activation" against the alternative hypothesis H_1, and rejects H_0 if $u>u_a$. This threshold which determines the significance degree of the results has been hitherto chosen heuristically by the investigators.

[¤]Correspondence: hamids@rad.hfh.edu

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We propose a method, based on randomization, to evaluate the statistical significance of the activations and to control the false detection rate in fuzzy cluster analysis of the fMRI. Making no specific assumptions about the noise structure, the randomization procedure can provide the distribution of "the membership degree to the active cluster (u)" under the null hypothesis (resting state condition). Using this probability density function, one can choose the required threshold u_a in order to control the false positive rate at level α. Using this approach, every active voxel will have a statistical significance (p value).

Clustering has been hitherto performed on the raw fMRI time series in most of the previous literature.[4,5] Because of poor signal-to-noise ratio (SNR) of the fMRI time series and confounding effects, the results of clustering on the raw time series are often unsatisfactory, and the FCM does not necessarily group data according to the similarity of their pattern of response to the stimulation. Moreover, increasing the dimension of the clustering space leads to practical difficulties such as "curse of dimensionality."

The use of an appropriate feature space extracted from the fMRI time-series alleviates these problems. The feature space defined by the cross-correlation of a fixed reference pattern and the fMRI time-series has been conventionally used for cluster analysis of the fMRI data.[6] Wavelets, due to their known advantages such as localization in time and frequency, have shown their ability in feature extraction. Scarth[7] applied the fuzzy cluster analysis to the wavelet transform of the time series and reported lower sensitivity to noise and artifacts. Here, we propose activation detection in wavelet domain. Combining the wavelet coefficients with our prior knowledge of the activation paradigm provides a feature space. Then, FCM clustering is applied to the resulting feature space and the cluster with the most similar centroid to the stimulation pattern is considered as the active cluster. This method can also be applied in the scalar wavelet domain.

We use the proposed approach for controlling the false positive rate to construct a novel model-independent fMRI activation detection method. The proposed method for controlling the false positive rate is applicable to any clustering algorithm using any feature space and yields statistically meaningful results. It allows application and comparison of different clustering methods and feature spaces in fMRI data analysis. Using the proposed method, we compare the proposed feature space to the cross-correlation feature space.

2. DATA

2.1. Simulated dataset

For a realistic simulation of the fMRI data, computer generated "activation" time series were added to the measured time series of a single slice of a resting state experimental fMRI data in 116 voxels and with different contrasts (1%, 1.5%, 2%, and 2.5%). The activation time series was obtained by convolving a stimulation pattern (a boxcar function with five periods of 60 seconds ON and 90 seconds OFF) with a gamma function that models the hemodynamic response function (HRF). In order to model the variability of the HRF, the parameters of the gamma function were varied randomly between different activated voxels. Fig. 1 shows the spatial locations of the active voxels.

2.2. Experimental dataset

Functional images were acquired from 6 normal volunteers using a single-shot GRE spiral scan sequence (TR=2 sec, TE=30 ms, FOV=220×220×96 mm^3, matrix size=64×64×24) on a 3 Tesla GE MRI scanner (General Electric, Milwaukee, WI, USA). The subject performed a finger tapping task with both hands. The task consisted of 12 periods of 36 seconds, where each period contained 18 seconds of finger tapping, followed by 18 seconds of rest. The first four volumes of the functional images were discarded and the remaining volumes were motion corrected using the AFNI software package.[8] Linear drifts and mean components were then removed from each voxel time-series.

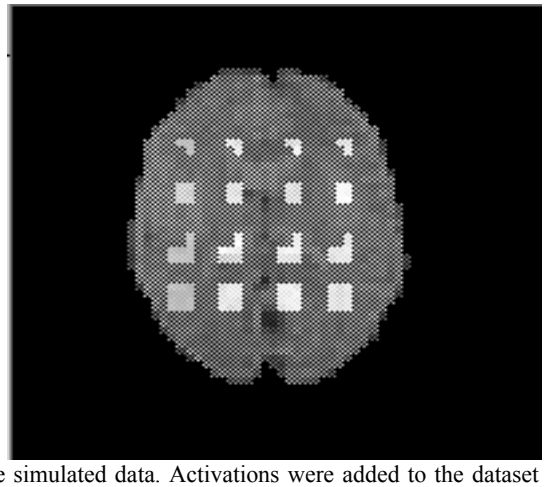


Fig. 1. Spatial pattern of activity in the simulated data. Activations were added to the dataset in the regions shown. The activation contrasts for the columns (from left to right) are 1%, 1.5%, 2% and 2.5%, respectively.

3. METHODS

Existence of significant noise and artifacts in the fMRI signal complicates the problem of activation detection in the time domain. We propose a wavelet decomposition of the signal to decrease the influence of these interfering components. Then a fuzzy clustering algorithm with controlled rate of false positive is applied on the features extracted from the wavelet coefficients.

The proposed method consists of the following four steps:

1) Feature Extraction: Wavelet coefficients of each fMRI time series are derived. A weighted average of coefficients of each time series is then considered as a feature. The weights are proportional to the wavelet coefficients of a reference signal. This reduces the effect of noise and artifacts.
2) Fuzzy Clustering: The FCM clustering is applied to the features obtained in Step 1 with the number of clusters obtained from the method proposed in.[4] After the FCM converges, the cluster with the centroid most similar to the activation pattern is chosen as the active cluster.
3) False Alarm Rate Control: Using randomization in the wavelet domain and fixing the center of the active cluster, the probability density function of the brain a voxel's "membership degrees in the active cluster" (u) under the null hypothesis, i.e., $Prob\{u|H_0\}$, is estimated. Then, a "membership degree threshold" (u_a) corresponding to the desired false alarm rate (FAR) is computed such that $Prob\{u>u_a \mid H_0\} = \alpha$.
4) The membership degrees in the active cluster map are thresholded with u_a in order to obtain an activation map.

3.1. Feature extraction

A high dimensional feature space may lead to practical difficulties such as "curse of dimensionality," especially when the length of the acquired fMRI time series is increased. Therefore, a feature extraction step is added to combine the large number of wavelet coefficients.

In order to obtain a feature for each time series we combine the features with weights proportional to the wavelet coefficients of the reference signal. In fact, we are interested in the similarity between the coefficients of the time series and that of the reference signal. The reference signal R is the expected pattern of activation, and can be computed by

convolving the pattern of stimulation and a conventional hemodynamic response function, such as a gamma function. Thus, for each time series, X_i, we find the corresponding feature, C_i, given by:

$$C_i = \frac{< DX_i, DR_e >}{\sqrt{< DX_i, DX_i >}} \tag{1}$$

$$DR_e = \frac{DR - Mean(DR)}{\|DR - Mean(DR)\|} \tag{2}$$

where DX_i is the wavelet coefficients of X_i and DR is the wavelet coefficients of R.

3.2. Fuzzy clustering

The well known fuzzy C-means (FCM) clustering algorithm is then applied to the features obtained in the previous step. One of the key problems in clustering is to determine the number of clusters *a priori*. In this paper, we use the cluster validity measure proposed by Fadili *et. Al*.[4] We also use the fuzziness index m=2 as suggested in Reference.[4] After the FCM converges, the cluster with the most similar centroid to the reference pattern is chosen as the active cluster. In the case of the proposed feature space, this is the cluster with a centroid that has the maximum value of C.

3.3. False alarm rate control

By comparing u at each voxel with u_a one tests the null hypothesis H_0: "no activation" and rejects H_0 if $u>u_a$. For controlling the type I error of this test at level α, a threshold u_a must be found such that $prob(u>u_a \mid H_0) = \alpha$. This requires the probability density function (pdf) $f_u(u|H_0)$, which is difficult to derive theoretically (analytically). We propose a method based on randomization for finding this pdf. In this research, we use the resampling procedure introduced by Bullmore *et. Al*,[8] which permutates the wavelet coefficients of the fMRI time series in order to make surrogate data under the null hypothesis. The wavelet coefficients (obtained using Daubechies basis with 4 vanishing moments) of the fMRI time series are permutated at different levels of resolution (in 4 levels), and then an inverse wavelet transform is applied on them to generate various realizations of data under the null hypothesis. The FCM is then applied on each set of the randomized data while we keep the center of the active cluster found before randomization unchanged, and then the membership degrees of all voxels in the active cluster are computed. These values construct an empirical histogram which estimates the required pdf $f_u(u|H_0)$. Using this histogram, one finds a threshold corresponding to the desired α. Thresholding the "active cluster membership map" of the brain voxels with this threshold generates statistically meaningful results. This step is needed when we intend to compare detection accuracy of different feature spaces.

4. RESULTS

An estimate of the false alarm rate of an fMRI detection method can be made by applying the method to the resting state data. In order to provide the resting state data, time series of activated voxels were discarded from each of the 6 fMRI experimental data. After computing the cross-correlation map for each data, the active voxels were detected for false alarm rate of 0.1, and their time series were discarded from the data. This ensures that the remaining voxels are in the resting state. The proposed method, explained in Section 3.2, was applied on each resting state data, and activated voxels were detected by assuming different false alarm rates. An estimate of the actual (occurred) false alarm rate was then made in each case by dividing the number of detected voxels to the number of voxels in the analyzed resting state data. Fig. 2 graphs the expected false alarm rate versus the observed (measured) false alarm rate for one of the 6 subjects. Table 1 shows the numerical values of theses parameters for all of the 6 subjects. This figure demonstrates the ability of our proposed method to control the false positive rate. In fact, using the pdf of u under the null hypothesis for choosing the threshold is the main foundation for controlling the false positive rate. One of the estimated pdf's is shown in Fig. 3.

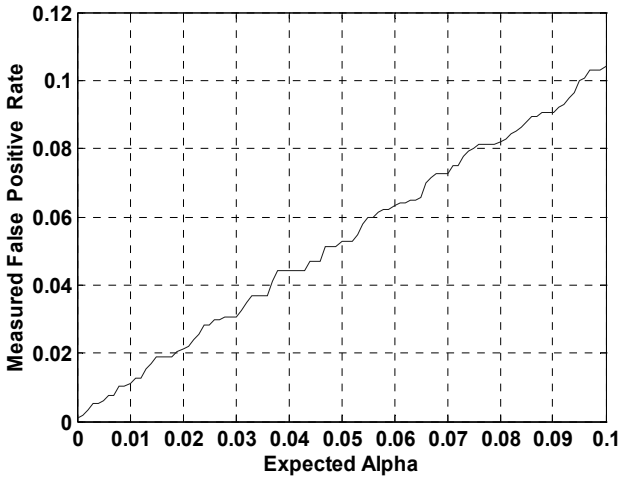


Fig. 2.The measured false positive rate versus its expected value in one of the 6 subjects.

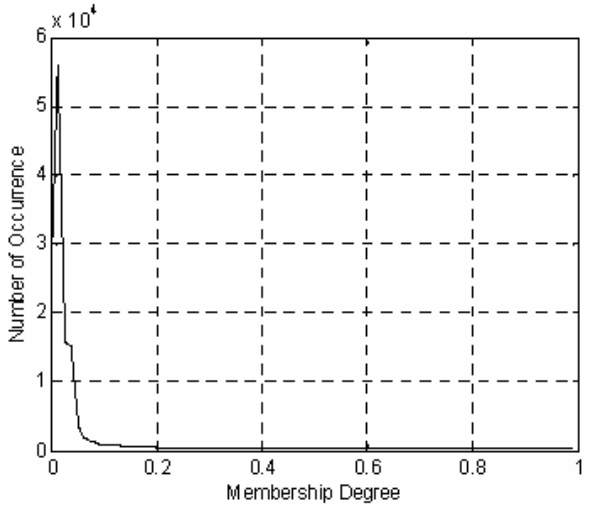


Fig. 3. Empirical histogram of the "membership degrees to the active cluster" under the null hypothesis, obtained by randomization in one of the experimental datasets. This histogram is used as an estimate of $f_u(u|H_0)$ for the subject.

To choose the optimal wavelet basis, we examined different wavelets on a simulated dataset with various false alarm rates. Fig. 4 shows the number of true detected pixels at various false alarm rates for db4, coif4, bior5.5, and sym8. As seen, the db4 wavelet reveals the best detection accuracy. In addition, trends and activation patterns are further apart in the db4 feature space as compared to the other wavelet feature spaces. A comparison is also made between the results of applying different methods: 1) db4 wavelet feature space; 2) cross correlation feature space (CC); and 3) Conventional Cross-correlation analysis. Fig. 5 shows the results. It can be seen that db4 surpassed the detection accuracy of the other feature spaces. Fig. 6 shows activation maps resulted from cross-correlation feature space and db4 wavelet feature space for false alarm rate of α=0.005. We also applied the proposed method to 6 finger-tapping fMRI datasets. We found that the proposed method detects more activated voxels in the expected regions (SMA, SMC, and Cerebellum) as compared to the CC feature space. Fig. 7 shows the detected activation regions superimposed on the anatomical images for one of the subjects.

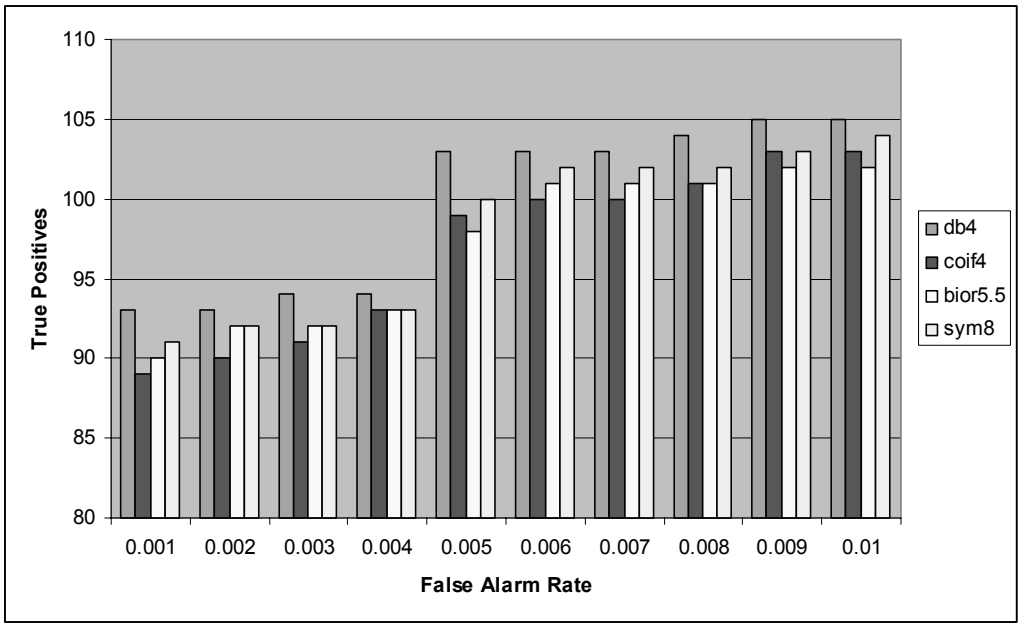


Fig. 4. Comparison of different wavelets: Number of true detected pixels at various false alarm rates for db4, coif4, bior5.5 and sym8.

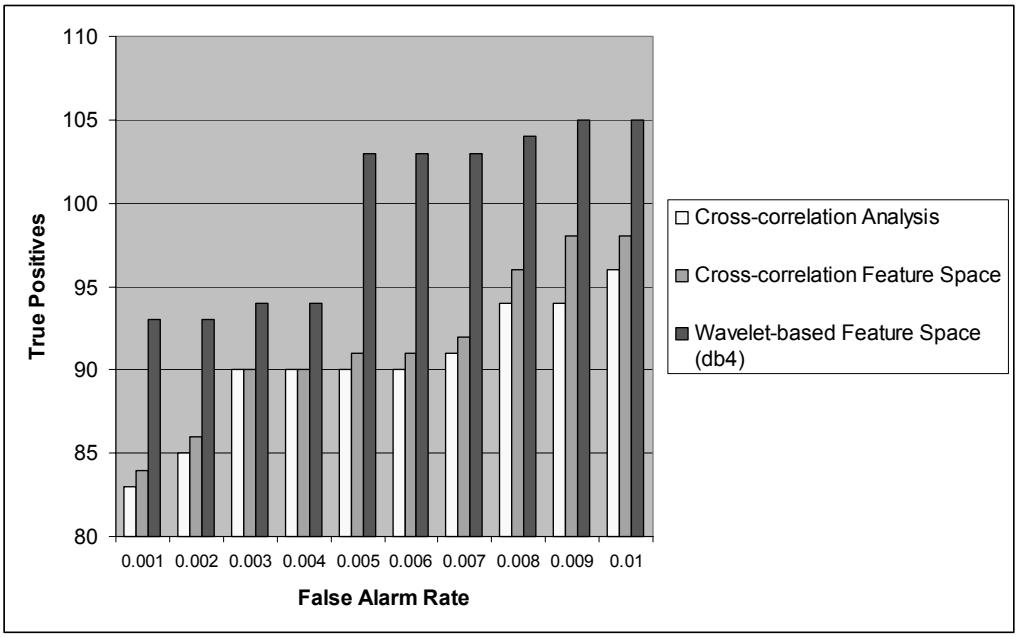
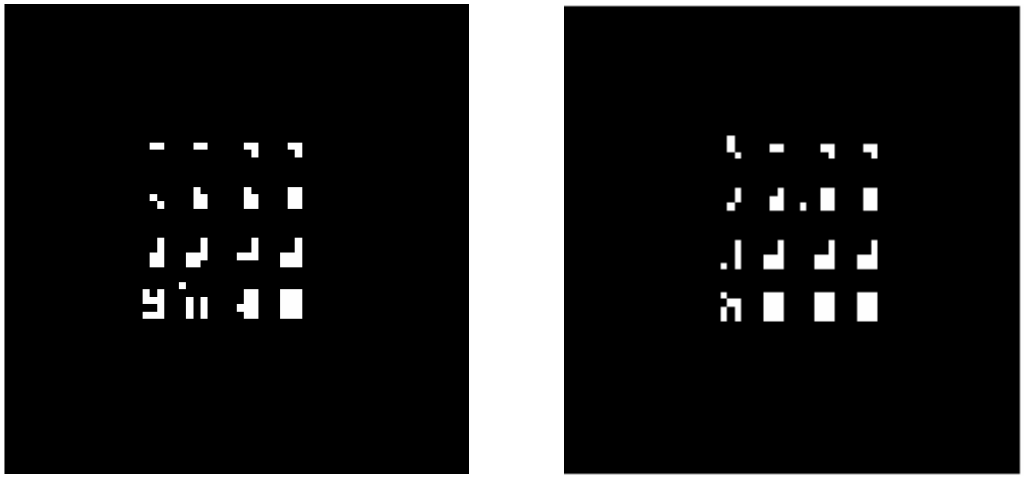


Fig.5. Comparision of different methods: Number of true detected pixels at various false alarm rates for the cross-correlation analysis, cross-correlation feature space, and wavelet-based feature space (db4).



(a) (b)

Fig. 6. Activation maps resulted form two different methods for false alarm rate of α=0.005: a) cross-correlation feature space, b) db4 wavelet feature space.

Table 1. Numerical values for Expected alpha value versus observed false alarm rate for 6 subjects.

Alpha (Expected)	subject 1 (Observed)	subject 2 (Observed)	subject 3 (Observed)	subject 4 (Observed)	subject 5 (Observed)	subject 6 (Observed)
0.01	0.0102	0.0108	0.0102	0.0119	0.0111	0.0111
0.02	0.0196	0.0197	0.0196	0.0222	0.0209	0.0213
0.03	0.0307	0.0307	0.0299	0.0324	0.0298	0.0307
0.04	0.041	0.0418	0.0392	0.0469	0.0444	0.0444
0.05	0.0503	0.0512	0.0496	0.0503	0.0529	0.0518
0.06	0.0597	0.0614	0.0597	0.064	0.0631	0.0631
0.07	0.07	0.069	0.07	0.0694	0.0725	0.0725
0.08	0.0802	0.0811	0.0785	0.0833	0.0811	0.0819
0.09	0.0896	0.0904	0.0887	0.093	0.0904	0.0904
0.1	0.0998	0.1024	0.099	0.1058	0.1038	0.1041

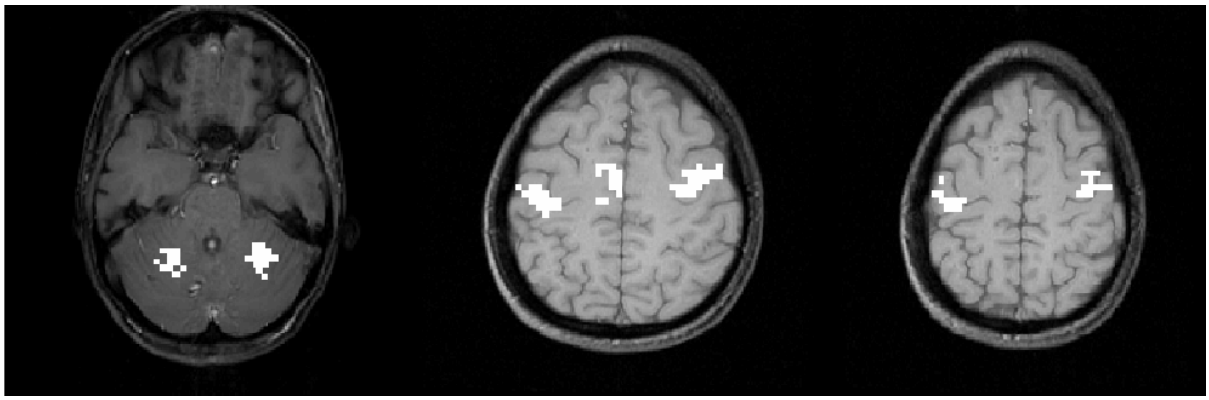


Fig. 7. Detected activation regions using the proposed method with db4 and 4 levels of decomposition at α=0.005, superimposed on the anatomical images for one of the subjects.

5. DISCUSSION AND CONCLUSION

A method for controlling false positive rate in the cluster analysis of the fMRI data was proposed and its efficiency was evaluated by activation detection using the FCM on 6 rest fMRI datasets. The result of analyzing the resting state datasets confirmed the ability of the proposed method to control the false positive rate. This is obtained at the expense of the complex computation needed. Fixing the false positive rate in activation detection using FCM makes it possible to compare the FCM with the other fMRI activation detection methods. One can also evaluate and compare the performances of different FCM-based methods, such as using different feature spaces. An accurate comparison between the above methods can not be made without considering the statistical significance of the results. The proposed method controls the rate of false positive occurrence without any assumptions about the noise or activation pattern at the expense of computational complexity of randomization. Using this method, we compared two feature spaces: cross correlation feature space; and wavelet-based feature space. Detecting more activated voxels in the same regions at the same false alarm rates shows superior sensitivity of the proposed method. This superiority stems from the multi-resolution decomposition of the wavelet transform that concentrates the activation components in specific levels while spreading the random noise in all levels almost equally. In addition, the proposed method when compared to the conventional cross-correlation method showed a higher sensitivity.

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